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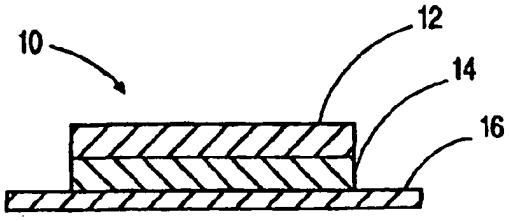
(54) Title: CONTACT ADHESIVE EXTENDS WEAR TIME ON SKIN

(57) Abstract

A pressure sensitive adhesive composition includes a hydrophobic polymer and an inorganic additive that is capable of absorbing water up to 200 % of inorganic additive weight. The pressure sensitive adhesive is particularly useful for adhesion to human skin for extended times, and is therefore particularly suitable for use in extended-wear adhesive transdermal delivery devices. Also, an adhesive transdermal delivery device (10) has an adhesive layer (14) including such an adhesive composition.



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CONTACT ADHESIVE EXTENDS WEAR TIME ON SKIN

Background

Technical Field

This invention relates to adhesive compositions for extended wear adhesion to human skin, and particularly to adhesive compositions for affixing transdermal delivery devices to human skin.

Background Art

An acceptable adhesive for application to human skin should have a number of properties not demanded in other applications. Particularly, adhesives for use on human skin should adhere immediately on contact, should be capable of maintaining good adhesion over an extended period of wear (preferably without causing excessive irritation to the skin), and should upon removal release from the surface without excessive damage to the skin and without leaving a residue. Such adhesives must be capable of adhering well in the warm, moist environment prevailing on human skin.

Many hydrophobic polymer adhesives such as acrylic adhesives are commonly used for affixing objects such as adhesive bandages or transdermal delivery patches to the skin. Most of these polymer adhesives tend to debond in the presence of moisture. As a result, the wear time on human skin of objects employing hydrophobic polymer adhesives, particularly acrylic adhesives, is typically four days' time or less.

A number of examples may be cited of acrylic polymer adhesive formulations proposed for improved adhesion in the presence of moisture.

Japanese patent publication no. JP 2078614 describes using a combination of a hydrophobic pressure sensitive adhesive and a hydrophilic

pressure sensitive adhesive, made up of poly(vinyl) pyrrolidone and glycerol, for adhesion of a variety of "soft" materials.

U.S. Patent No. 4,701,509 describes improved adhesion in the presence of moisture using a hot-meltable composition that includes a copolymer of acrylate monomers and a vinyl caprolactam.

European patent publication EP 140941 describes improved adhesion in the presence of moisture using a composition containing a copolymer of a hydrophobic ester monomer, a hydrophilic vinyl monomer and a polar comonomer.

It can be advantageous in some applications, for example for transdermal delivery systems, to provide extended wear time, up to one week's time or longer.

Summary of the Invention

We have discovered that the adhesion of hydrophobic polymer pressure sensitive adhesive compositions in the presence of moisture can be improved by adding to a hydrophobic polymer adhesive an appropriate quantity of an inorganic additive having the capacity to absorb water to a significant percentage of its weight. The resulting adhesive can provide for extended wear time on human skin, as compared with the wear time of the acrylic polymer adhesive not having the inorganic additive. Over extended wear times, adhesives according to the invention have improved adherency characteristics and, additionally, display improved aesthetic or cosmetic appearance.

Suitable additives include, for example, hydrophilic inorganic compounds which absorb or adsorb a large percentage of their weight of water. These compounds have a particle size between about 3 and 100 microns, preferably between about 4 and 10 microns and include, for example, silica gel, calcium silicate, and magnesium silicate. The inorganic hydrophilic additives are combined with the polymer adhesive according to

the invention in proportions between about 2 % and about 20 % by weight of polymer. The dynamic viscosity (measured at lower frequency) of the mixture of the hydrophobic polymer adhesive and the inorganic additive according to the invention preferably is less than, or is not substantially (no more than about 60 %) greater than, that of the adhesive alone; and more preferably the dynamic viscosity of the mixture of the hydrophobic polymer adhesive and the inorganic additive is less than 50 % (more preferably less than 40 %) greater than that of the adhesive alone. Preferably the dynamic viscosity of the mixture of adhesive and additive is not substantially (preferably less than about 3 fold) decreased by exposure of the adhesive/additive mixture to moisture (100 % humidity for 24 hours).

The preferred formulation may vary according to the particular inorganic hydrophilic additive used. In one example, silica gel was combined with an acrylate adhesive ("Morstik 607") in a proportion by weight of 10 % silica gel and 90 % Morstik; the resulting product showed greater than 80 % of initial adhesion and retained an acceptable aesthetic appearance over a 7 day period.

Disclosure of the Invention

Accordingly, in one general aspect, the invention features a pressure sensitive adhesive composition containing a hydrophobic polymer and an inorganic additive that is capable of absorbing water up to 200 % of inorganic additive weight. By hydrophobic is intended a material that will not absorb water by more than 5 %.

Preferably the inorganic hydrophilic additive and the polymer are present in the composition in a proportion between 2 % and 20 % by weight of additive to polymer. Addition of the inorganic hydrophilic additive according to the invention does not substantially change the cohesive strength of the adhesive and, particularly, it does not result in a substantial increase in the cohesive strength of the adhesive.

Preferred hydrophobic polymers are pressure sensitive adhesives at ambient temperatures, and include polyisobutylene (PIB) or mixtures of PIB with polybutenes, and polyacrylates.

Preferred inorganic additives include, for example, silica gel, calcium silicate and magnesium silicate.

In another general aspect the invention features an adhesive transdermal delivery device having an adhesive layer that includes a pressure sensitive adhesive composition containing a hydrophobic polymer and an inorganic additive that is capable of absorbing water up to 200% of organic additive weight.

Description of Preferred Embodiments

Preferred embodiments of the invention will now be described, beginning with a brief description of the drawings.

Brief Description of the Drawings

Fig. 1 is a sketch, not to scale, showing an exemplary transdermal delivery device of the invention in transverse sectional view.

Fig. 2 is a graph showing the effect of various hydrophilic inorganic additives on the dynamic viscosity of a hydrophobic polymer adhesive.

Fig. 3 is a graph showing the effect of moisture on the dynamic viscosity of the Morstik adhesive, and the adhesive with an additive.

Figs. 4.1 - 4.3 are graphs showing wear performance characteristics of various transdermal delivery patches in an informal extended wear trial using adhesive compositions according to the invention. Fig. 4.1 shows adhesion; Fig. 4.2 shows the extent of border formation; and Fig. 4.3 shows the extent of irritation or erythema.

Modes of Carrying Out the Invention

Generally, the adhesive compositions according to the invention are made by mixing a selected inorganic hydrophilic additive with a selected hydrophobic adhesive in appropriate proportions. Preferably, mixing is facilitated by dispersing the inorganic hydrophilic additive in an appropriate cosolvent, then admixing the hydrophobic adhesive with the cosolvent-dispersed inorganic hydrophilic additive and agitating for a time sufficient to dissolve or disperse the adhesive and the additive to apparent homogeneity.

The adhesive composition can then be cast and dried to form a film; for use in a transdermal delivery device, the adhesive composition according to the invention can be applied to form an adhesive lamina according to standard techniques. Typically the contact surface of the adhesive lamina is covered with a release liner for protection. An exemplary transdermal delivery device according to the invention is shown by way of illustration generally at **10** in Fig. 1. Device **10** includes adhesive layer **14** having an upper surface covered by backing layer **12** and a basal surface covered by strippable release liner **16**. Adhesive layer **14** contains, according to the invention, an inorganic hydrophilic additive and a hydrophobic polymer adhesive. In a configuration such as is shown in Fig. 1, the adhesive layer **14** constitutes a delivery matrix, which contains the substance to be transdermally delivered, together with one or more suitable vehicles and/or penetration enhancers. As will be appreciated, one or more additional layers (not shown in the Fig.) may overly adhesive layer **14**, and may play any of various roles in the delivery system of the device. For example, one or more matrix layers may overly adhesive layer **14**, and in such a configuration the adhesive layer need not itself serve as a delivery matrix.

Whether or not adhesive layer **14** serves as a delivery matrix, its basal surface contacts the skin surface, and so any substance that is to be delivered from the device into and through the skin passes through adhesive layer **14**. Depending upon whether a substance to be delivered by the device

is itself more or less hydrophilic, the substance release rate may be modulated by the inorganic hydrophilic additive in the adhesive layer.

The following examples illustrate the invention.

Example I

Dynamic Viscosity of Adhesive With Additives

The dynamic viscosities as a function of sampling frequency for an acrylic adhesive (Morstik 607, Montsanto Chemical) with four different silica gel additives (two, designated FP-74 and FP-63, from Grace Chemicals; one from Aldrich) were measured as follows. The adhesive was combined in the solvent with the silica gel additive to 10 % w/w silica gel:Morstik 607. The resulting mixture (adhesive + additive + solvent) was cast on a release liner and the solvent was evaporated, and the resulting dry film was pressed to approximately 2 to 3 mm thickness. A disc of diameter about 1 inch (about 2.54 cm) was cut from the pressed dry film, and sandwiched between the parallel plates of a Rheometrics Mechanical Spectrometer, Version 800 ("RMS-800"). The sample was melted and the dynamic viscosity was measured as a function of frequency according to standard procedures. The resulting data are plotted as viscosity versus frequency, producing a "dynamic viscosity spectrum".

The measured viscosity of the four tested compositions at four different frequencies is shown in Table I.

Table I

Viscosity of Acrylic Adhesive with and without silica gel Additives

Adhesive Formulations	Sampling Frequency, rad/sec			
	0.001	0.01	0.10	100
Morstik 607	4×10^7	8.5×10^6	1.8×10^6	2×10^4
Morstik 607 + 10 % Grace 74 FP	5×10^7	1.2×10^7	1.8×10^6	2.5×10^4
Morstik 607 + 10 % Grace 63 FP	1.8×10^7	7×10^6	1.8×10^6	2.5×10^4
Morstik 607 + 10 % Aldrich	4×10^7	1×10^7	2.8×10^6	3×10^4

With respect to the dynamic mechanical properties of pressure sensitive adhesives, the viscosity (or modulus) at lower frequencies is generally understood in the adhesives art to be of greatest significance in the wetting or adhesion process. *See, e.g.*, L.-H. Lee, Ed. (1991), *Adhesive Bonding*, Plenum Press; particularly, *e.g.*, Chapter 5, pp. 133-36. Thus, typically, viscosity or modulus values are quoted at 0.1 rad/sec or 0.01 rad/sec as being a critical parameter.

Adhesive polymers that are within "holding strength" (or cohesive strength) specifications vary substantially from lot to lot in viscosity. The dynamic viscosity of Morstik 607, as supplied by the vendor, varies by as much as 50 % to 60 % at frequencies of 0.01 rad/sec or 0.1 rad/sec. Adhesives from these variable lots perform adequately for their purpose as a pressure sensitive skin contact material. Thus, while the acceptable range within which addition of an inorganic additive according to the invention may be permitted to vary the viscosity of the base polymer without

unacceptably changing the cohesive strength of the adhesive, is difficult to quantify. Generally, increase of the viscosity by as much as about 60 % (for example, for Morstik 607) by addition of the additive can be expected not to substantially degrade pressure sensitive adhesive properties.

Fig. 2 shows the dynamic viscosity spectra for samples of Morstik 607 alone (filled circles) and for Morstik 607 combined with 10 % of the silica gel additives, indicated as follows: Grace 74 FP, open circles; Aldrich, triangles; Grace 63 FP, X. Using a frequency of 0.01 rad/sec as a reference, the viscosities of the samples with silica gel added to the adhesive are either lower than for the adhesive alone, or are substantially the same as for the adhesive alone (within about 20 % for the Aldrich silica gel, or within about 40 % for the Grace 74 FP, for example). Such differences are well within the range of acceptable variation in viscosity of such polymer adhesives as supplied without additives.

Adhesive patches constructed using an adhesive according to the invention, containing Morstik 607 with silica gel additives, show extended wear over 7 days, as shown for example in Fig. 4.1.

Example II

Effect of Moisture on Dynamic Viscosity of Adhesive With Additives

For this example, an adhesive film according to the invention was constructed using as a hydrophobic polymer Morstik 607 and using the Aldrich silica gel as an inorganic additive, and the dynamic viscosities as a function of sampling frequency were compared for the film when dry and when moistened. The Morstik 607 adhesive was combined in the solvent with the Aldrich silica gel additive to 10 % w/w silica gel:Morstik 607. The resulting mixture (adhesive + additive + solvent) was cast on a release liner and dried. The wet layer thickness was calculated to yield a dry film of about 0.5 mm thickness. A disc of diameter about .4 in (about 1 cm) was

cut from the pressed dry film, and sandwiched between the parallel plates of a RMS-800. The sample was melted and the dynamic viscosity was measured as a function of frequency according to standard procedures.

The dynamic viscosity was measured both in dry discs cut from the adhesive mixture and in discs that had been exposed to 100% humidity for about 24 hours. The resulting dynamic viscosity spectra are shown in Fig. 3. As can be seen, exposure to moisture does not change the viscosity by more than a factor of 3.

Example III

Adhesive Compositions

Adhesive compositions were made by admixing hydrophilic additives selected from those tested in Example I with a variety of acrylic adhesives, as follows. First, the selected additive was dissolved or dispersed in a cosolvent to facilitate mixing, and then the selected acrylic adhesive was added and mixed to homogeneity.

Any of a variety of hydrophobic polymer adhesives may be used according to the invention, including polyacrylates, polyisobutylene (PIB) or mixtures of PIB with polybutenes. The polyacrylates are copolymers of the following monomers: methyl acrylate, 2-ethylhexyl acrylate, vinyl acetate, acrylic acid, butyl acrylate and hydroxy-ethyl acrylate. Further, block copolymers of styrene/isoprene/styrene, styrene/butadiene/styrene and styrene/ethylene-butylene/styrene with suitable other resins and tackifiers are preferred hydrophobic polymers. Many acrylic polymers are commercially available. They include, for example, various acrylate polymers distributed by Morton Thiokol, Inc. under the tradename Morstik, or distributed by National Starch and Chemical Company under the tradename DuroTak, or distributed by Monsanto Chemical Company under the tradename Gelva. Morstik 607 (Morton Thiokol, Inc.), Gelva 737 (Monsanto Chemical Company), or DuroTak 280-1516 (National Starch and Chemical Company).

These acrylate polymers are suitable according to the invention for admixture with a hydrophilic additive such as calcium silicate.

A suitable cosolvent may be selected form the list of solvents for the adhesive. The additive must be freely dispersible in the solvent. Isopropyl alcohol or ethanol or ethyl acetate, for example, can be suitable according to the invention for facilitating admixture of calcium silicate in proportions up to 20 % by weight with Morstik.

Example IV

Placebo Transdermal Devices

Adhesive devices employing adhesive formulations according to the invention (but not containing a substance to be delivered: "placebo patches") were constructed and tested in a human extended wear study as follows.

Morstik 607 was combined with two different silica gels (Grace Chemical 63FP and Aldrich Chemical Silica Gel), 10% by weight. The components were mixed to apparent homogeneity, then spread on a backing layer to a thickness of about 10 mils and dried to a thickness of about 5 mils. The same procedure was repeated for Morstik 607 without the additive.

The resulting backed adhesive film was die-cut to form patches having an area of about 5 cm^2. In addition, a 30 cm^2 patch was also made with the Aldrich Silica Gel. One such patch was applied on day 0 to the dry normal skin of each upper arm of 9 human volunteers. The patches and underlying skin were observed and photographed on each of days 3, 4, 5, 6 and 7. The results are shown in Figs. 4.1 through 4.3, showing adhesion characteristics, and skin condition of the subjects.

As Fig. 4.1 shows, the patches containing silica gel maintained adhesion well above an acceptable 80% adhesion standard over the 7-day period of the study. Adhesion of the "placebo" patch containing just Morstik 607, however, showed a drop below 80% by day 3. Fig. 4.2

shows the extent of "border" formation, or excess adhesive flow around the patch edge, which is also an aesthetic criterion. Since 4 mm is the acceptable aesthetic limit, the patches containing silica gel were well within the acceptable range. Figure 4.3 shows the irritation or erythema levels of the patches containing silica gel. Since 2 is the acceptable limit, all the patches were acceptable with regard to erythema as well.

Example V

Adhesive Transdermal Delivery Devices

Adhesive transdermal delivery devices according to the invention can be conventionally constructed, using the adhesive formulation of the invention. In some device configurations, the adhesive layer acts as a delivery matrix, and such devices can be constructed for example by combining a substance (or substances) to be delivered with the combined acrylic polymer and inorganic hydrophilic additive prior to spreading and drying the adhesive film. It may be advantageous, depending upon the nature of the substance or substances to be delivered, additionally to combine one or more vehicles and/or enhancers with the adhesive matrix formulation.

Any substance that can be administered transdermally can be delivered using an adhesive transdermal device according to the invention. These include anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics, antihelminthics, antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers, beta-blockers such as pindolol, anti-arrythmics, antihypertensives, diuretics, and vasodilators

including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including antihistamine decongestants; hormones such as the estrogens estradiol and progesterone and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedative; and tranquilizers.

Particularly, the invention is useful for continuous or pulsed or variable rate delivery over extended periods of time, up to and exceeding one week. Substances that may be advantageously administered in an extended time regime include, for example, steroid drugs, including progestogens such as norethindrone, norethindrone acetate, desogestrel, 3-keto desogestrel, gestadene and levonorgestrel; estrogens such as estradiol and its esters, *e.g.*, estradiol valerate, cyprionate, deconate and acetate, as well as ethinyl estradiol; androgens such as testosterone and its esters; and corticosteroids such as cortisone, hydrocortisone, and fluocinolone acetonide. For some therapies, the device contains and delivers a combination of one or more estrogens, particularly estradiol, and may additionally contain and deliver one or more progestogens.

Other Embodiments

Other embodiments are within the following claims.

Claims

1. A pressure sensitive adhesive composition comprising a hydrophobic polymer and an inorganic additive that is capable of absorbing water up to 200 % of inorganic additive weight, the dynamic viscosity of said composition containing said inorganic additive being substantially the same as or less than the dynamic viscosity of such a composition not containing said inorganic additive.

2. The pressure sensitive adhesive composition of claim 1, wherein said inorganic additive is present in a proportion in the range about 2 % to about 20 % by weight of said hydrophobic polymer.

3. The pressure sensitive adhesive composition of claim 1, wherein said inorganic additive is present in a proportion in the range about 5 % to about 10 % by weight of said acrylic polymer.

4. The pressure sensitive adhesive composition of claim 1, wherein said inorganic additive is one of silica gel, calcium silicate and magnesium silicate.

5. The pressure sensitive adhesive composition of claim 1, wherein said hydrophobic polymer is an acrylic polymer.

6. An adhesive transdermal delivery device, having an adhesive layer made up of the adhesive composition of claim 1.

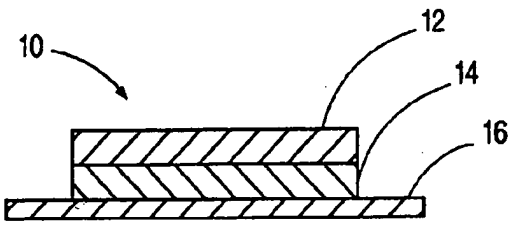

FIG. 1

FIG. 2

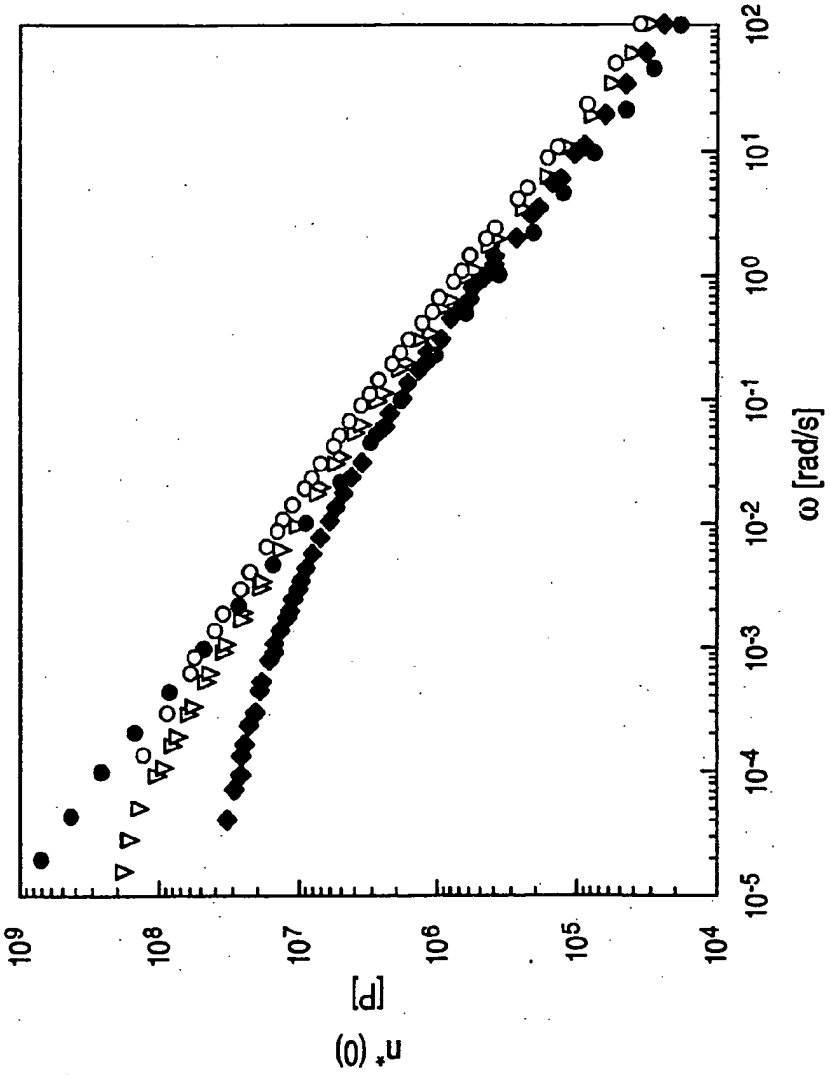
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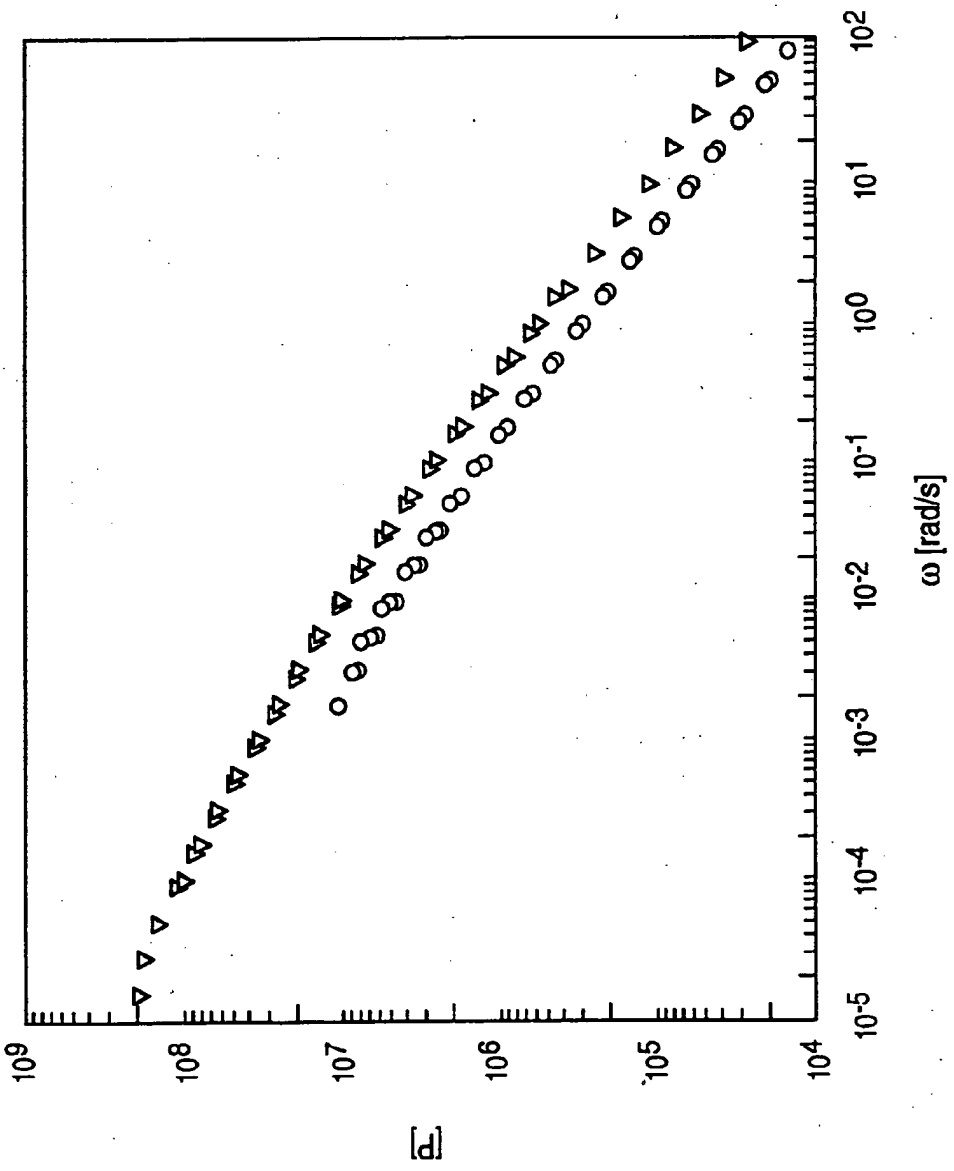
FIG. 3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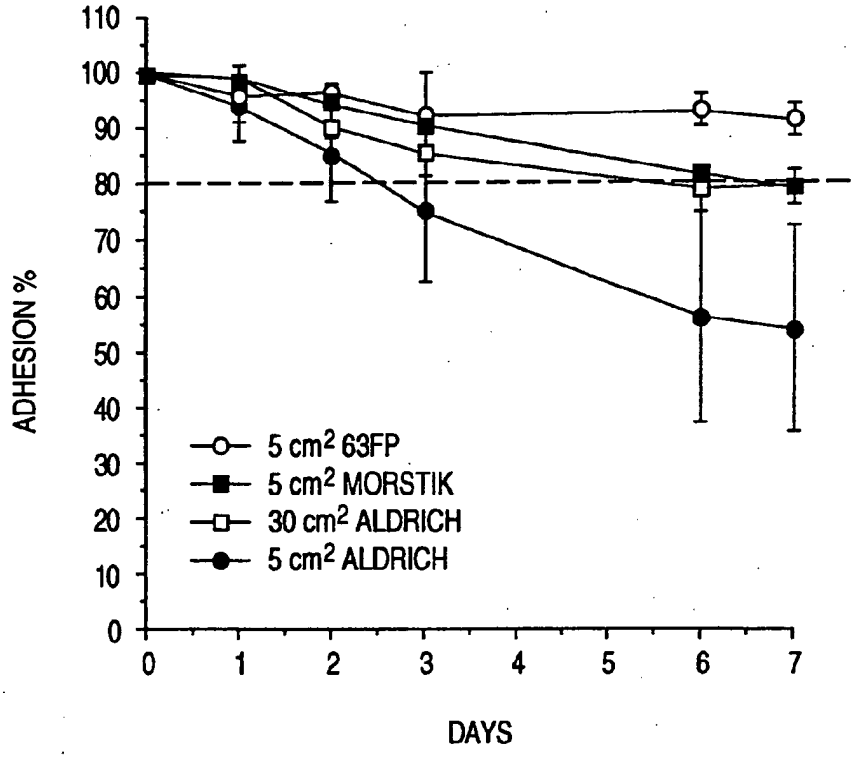
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1
2
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DAYS
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5 cm2 MORSTIK
30 cm2 ALDRICH
5 cm2 ALDRICH

FIG. 4A

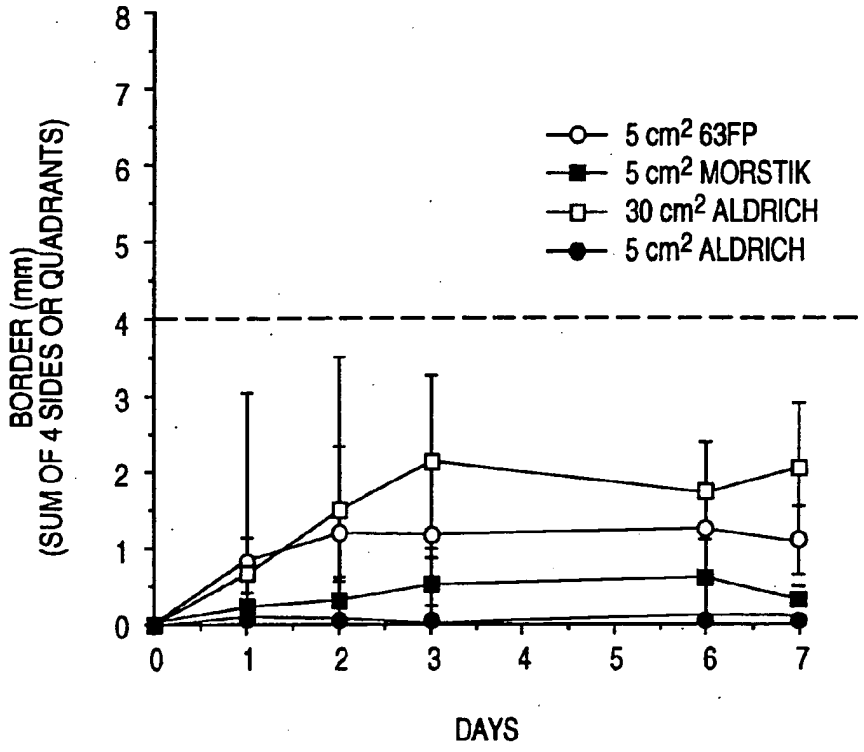
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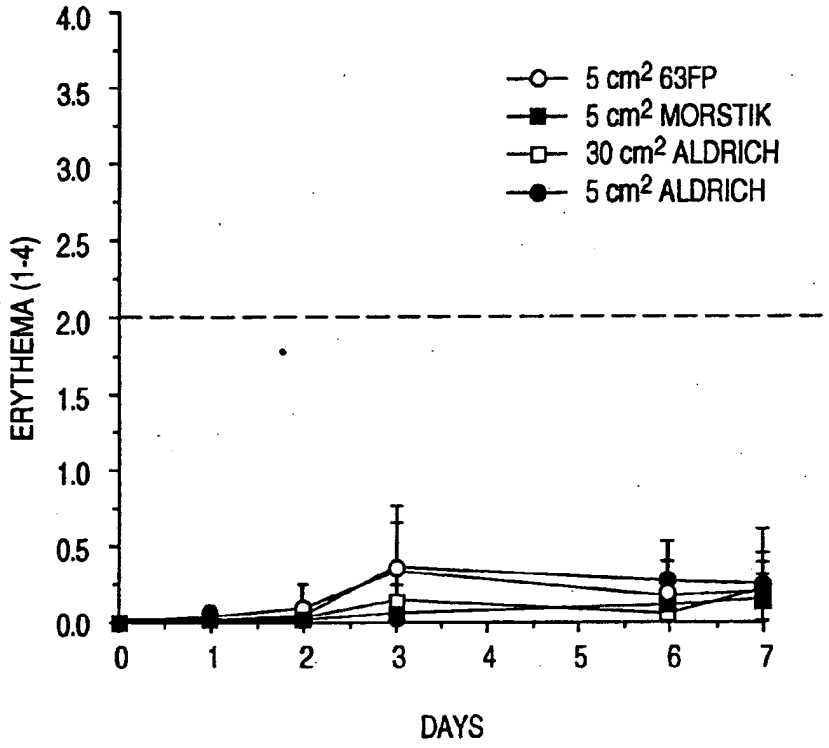
FIG. 4B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3
4
5
6
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DAYS
5 cm2 63FP
5 cm2 MORSTIK
30 cm2 ALDRICH
5 cm2 ALDRICH

FIG. 4C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09249

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61F, 13/00, 13/02; C08K 3/34, 3/36

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 449; 523/111; 524/442, 445, 447, 448, 449, 450, 451, 456, 492, 493

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,918,128 (SAKAI) 17 April 1990. See Abstract and claims 1-3.	1-5
X, P	US, A, 5,260,064 (NAKAGAWA ET AL) 09 November 1993. See Abstract and column 6, lines 17-30	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 OCTOBER 1994	Date of mailing of the international search report 14 NOV 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PETER A. SZEKELY Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09249

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/448, 449; 523/111; 524/442, 445, 447, 448, 449, 450, 451, 456, 492, 493